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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,546	11/12/2003	Joseph S. Podolski	07189.0028.CPUS02	9175

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,546	PODOLSKI ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/06/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 10-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, with the Group II(a), claims 4 and 10-14, is acknowledged.

Status of Application

2. By Amendment filed December 06, 2005, claims 1-3 and 5-9 have been cancelled; claims 10, 12-14 have been amended; and claims 15-19 have been newly added. Claims 4, 10-19 are currently pending for prosecution on the merits.

Information Disclosure Statement

3. The information disclosure statement filed October 19, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4 and 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a symptom of wasting related to the specific medical condition, with the administration of a composition comprising cis-clomiphene and transclomiphene or pharmaceutically acceptable salts, for example

wasting in HIV infected patient, does not reasonably provide enablement for "treating wasting in a mammal...analogs thereof...solvates thereof". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention is drawn to a method of treating wasting in mammal comprising administering a composition comprising cis-clomiphene and tran-clomiphene or analogs thereof or pharmaceutically acceptable salts or solvates thereof, wherein the ratio of trans-clomiphene to cis-clomiphene is greater than 71/29. The term "wasting" is recognized in the art as "any general reduction in vitality and strength of body and mind resulting from a debilitating chronic disease" or "a decrease in size of an organ by disease or disuse" (see thefreedictionary.com or Dorland Online Medical Dictionary). In other

words, the instant invention relates to a method of treating various medical conditions associated with symptoms of wasting by administering said clomiphene composition.

There are no known compounds of similar structure that have been demonstrated to treat or control the entire scope of medical condition associated with "wasting". Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "magic bullet" is contrary to our present understanding of pharmacology. It is beyond the skill of pharmacologists today to get an agent to treat the conditions or diseases encompassed by the claimed invention.

The relative skill of those in the pharmaceutical art is high. The unpredictability of the pharmaceutical art is very high. As stated above, applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant composition. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The claims are very broad. The scope of the instant claims encompasses treatment of multitude of disorders or conditions that may have unrelated manifestation. For instance, cachexia, aging, endocrine myopathies, paraneoplastic neuromyopathy, congenital myopathies, congenital myasthenic syndromes, myoglubinuria, polymyositis, brachial plexopahty, diabetic amyotrophy, Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), chronic wasting disease, denervation, wasting in HIV and etc…

The instant specification discloses that testosterone therapy has positive effects on the fat-free muscle mass, bone, memory, libido and sense of well-being in HIV-infected men are known in the art (para. [0008]). As the specific embodiment of the invention, the specification provides in vivo test of showing the activity of said composition in increasing testosterone level and assay methods in monitoring testosterone levels and change in muscle mass in HIV-infected individuals in subsequent to the administration of said composition (para. [0052]-[0053] and [0067]-[0068]). It appears in view of the instant specification, the instant invention links the testosterone enhancing activity of the instantly claimed clomiphene composition to the possible therapeutic utility in HIV-wasting. However, there is no demonstrated correlation that the tests and results apply to the treatment of all of the diseases or disorders embraced by the instant claims.

Although androgen (i.e., testosterone) is involved in pathophysiology of various medical conditions, for example erectile dysfunction, oligospermia or azoospermia, depressed mood, dementia, Alzheimer's Disease, hypogonadism, increased risk of osteoporosis, aging skin, atherosclerosis, hypercholesterolemia, hyperlipidemia, obesity, aplastic anemia, prostate cancer, and etc..., it is not known yet that a single underlying mechanism ties together all of the seemingly unrelated manifestations. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of said clomiphene composition.

Furthermore, the specification does not provide sufficient guidance in how to make/use vast number of possible analogs or solvates, other than clomiphene (racemic mixture of cis-clomiphene and trans-clomphene) and cis- and trans- isomers of

clomiphene. Since analogs and/or solvates of a pharmaceutical solid can have different chemical and physical properties, the skill artisan would have not known that which analogs or solvates are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation. The instant claims read on any analogs or solvates of cis- or trans- isomers of clomiphene or clomiphene that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Thus, the claimed invention necessitates an exhaustive search for the embodiments suitable to practice the claimed invention.

As discussed above, although the specification describes working examples of clomiphene (wherein the ratio of trans- clomiphene to cis-clomiphene is greater than 71/29) in increasing testosterone level in the body, there is no teaching in the specification that the administration of said composition would be able to accomplish the desired effect of the claimed invention encompassed by the instant claims. In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the unpredictability of the pharmaceutical art, it would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 4 and 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tenover et al. (The Journal of Clinical Endocrinology & Metabolism, 1987, abstract, Vol. 65, 1118-1126) in view of Applicant's admission of the prior art ([0008], and further in view of Baird (EP 0430388 A2).

Tenover teaches the activity of clomiphene (which is a mixture of two geometric isomers [cis (zuclomiphene) and trans (enclomiphene)] containing between 30% and 50% of the cis-isomer) in increasing serum testosterone levels in body.

Applicant's admission of the prior art acknowledges that testosterone therapy is beneficial in HIV-infected men and has positive effects on the fat-free muscle mass, bone, memeory, libido and sense of well-being in HIV-infected men.

Baird teaches the administration of clomiphene, substantially free of cis-isomer form, to mammal. The reference discloses that the use of the trans-isomer substantially free of the cis-isomer reduces potential toxicity and tetratogenic effects (page 3, lines 22-24).

The teaching Tenover differs from the claimed invention in (i) the use of said clomiphene composition in treating wasting in mammal, particularly patient infected with HIV (claims 12 and 14), (ii) the specific ratio of trans-clomiphene and cis-clomiphene, and (iii) the specific dosage amounts of trans-clomiphene per day, namely "a dosage of 1-200mg" (claim 15), "a dosage of 50mg" (claim 16), "a dosage of 1.5mg/kg of trans-clomiphene" (claim 17), "12.5mg" (claim 18); and the specific dosage form, for example a capsule (claim 19). To incorporate such teaching into the teaching of Tenover, would have been obvious in view of Applicant's admission of the prior art that provides the nexus between the involvement of testosterone and the therapeutic utility in the treatment of HIV-wasting.

One having ordinary skilled in the art would have expected that the modulation of testosterone level (by enhancing serum testosterone level) would provide beneficial effect on libido and sense of well being in HIV-infected men. Furthermore, one having ordinary skilled in the art would have expected that the administration of clomiphene known to increase serum testosterone levels in human would provide similar activity as the exogenous testosterone therapy. Thus, one having ordinary skilled in the art would have

been motivated to modify the teaching of Tenover with reasonable expectation of success to extend the usage of the claimed composition in human. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the specific ratio of trans-clomiphene to cis-clomphene, such determination of the specific ratio of cis-isomer and trans-isomer having optimum therapeutic index is considered obvious task for the skilled artisan. One having ordinary skilled in the art would have expected as taught by Baird that the administration of clomiphene, essentially in trans-isomer form, would provide effective treatment without the significant toxic effects.

In addition, those of ordinary skilled in the art would have been readily optimized effective dosages or dosage forms as determined by good medical practice and the clinical condition of the individual patient. Those of ordinary skill in the art will readily optimize effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the prior art.

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614